INTRODUCTION

Neonatal sepsis is one of the major health problems throughout the world. According to WHO approximately 5 million neonatal deaths occur each year worlidwide, 98% of which in least developed and developing countries ***(Campos et al., 2010).***

Sepsis can be considered an abrupt evolution of infections supported by a cytokine-mediated condition consisting of immune, inflammatory and coagulation homeo-stasis impairment ***(Chirico et al., 2011).***

Chemokines are chemotactic cytokines that give directional guidance for leukocyte migration ***(Christopher et al., 2007)***.

CXCR-4 is an alpha-chemokine receptor specific for stromal-derived-factor-1 (SDF-1 also called CXCL12), a molecule endowed with potent chemotactic activity for lymphocytes ***(Tamamis et al., 2014)***.

The roles of CXCL12 and CXCR4 in sepsis have not previously been identified, although recently, Ding et al. demonstrated that CXCR4 expression on the surface of circulating blood lymphocytes was up-regulated during sepsis ***(Ding et al. 2006)***.

AIM OF THE WORK

The purpose of this prospective study, case-control study was to evaluate the diagnostic and prognostic value of elevated CXCR4 in neonatal sepsis.

Chapter One

NEONATAL SEPSIS

Definition:

Neonatal sepsis or septicemia is a clinical syndrome characterized by systemic signs of circulatory compromise (e.g., poor peripheral perfusion, pallor, hypotonia, poor responsiveness) caused by invasion of the bloodstream by pathogenic microorganisms in the first month of life. In the pre-antibiotic era neonatal sepsis was usually fatal ***(Edmond and Zaidi, 2010).***

The term systemic inflammatory response syndrome (SIRS) is most frequently used to describe this unique process of neonatal infection and the subsequent systemic response. Neonates with SIRS have a spectrum with clinical symptoms that represent progressive stages of the pathologic process ***(Wynn et al., 2010).***

Table (1): Criteria for the Systemic Inflammatory Response Syndrome Two or more of the following are required:

1) Body temperature ≥ 38°C or ≤36°C
2) Heart rate >90 beats per minute
3) Respiratory rate >20 breaths per minute or arterial CO2 tension less than 32 mmHg or a need for mechanical ventilation
4) White blood count greater than 12,000/mm3 or _4000/mm3 or _10% immature forms.

(Remick, 2007)

Definitions of sepsis and septic shock not been established for preterm neonates. These patients present diagnostic challenges that are clouded by immaturity of organ systems and transitional physiology.

Largely because blood pressure alone cannot identify abnormal cardiac output, organ perfusion, and oxygen delivery. In the absence of normative values, the hemodynamic response to septic shock and optimum clinical interventions in preterm neonates are not well understood ***(Wynn and Wong, 2010).***

Table (2): Definitions of sepsis, severe sepsis, and septic shock:

- **Sepsis:** sepsis is defined as infection plus systemic manifestations of infection
- **Severe sepsis:** sepsis with sepsis-induced organ dysfunction or tissue hypoperfusion
- **Sepsis-induced hypotension:** a systolic blood pressure (SBP) less than 90mmHg or mean arterial pressure less than 70mm Hg, or an SBP decrease of greater than 40mm Hg or greater than 2 SD less than normal for age in the absence of other causes of hypotension
- **Septic shock:** sepsis-induced hypotension persisting despite adequate fluid resuscitation.
- **Sepsis-induced tissue hypoperfusion:** septic shock, lactate elevation beyond the upper limits of normal or oliguria
- **Acute oliguria:** urine output less than 0.5 mL/kg/h for at least 2 hours, despite adequate fluid resuscitation.

(Dellinger et al., 2008)

Epidemiology

Morbidity and Mortality of neonatal sepsis:

Neonatal sepsis remains a major cause of mortality and morbidity in the first year of life, Despite the considerable advances in modern treatments, It is still a leading cause of death in critically ill babies, with a mortality rate ranging from 1.5% in term to 40% in very-low-birth weight infants ***(Weston et al., 2011).***

Pathogenesis:

Neonatal infections are unique due to a number of factors:

1) There are diverse modes of transmission of infectious agents from mother to fetus or newborn infants as tran-haematogenous spread, Vertical transmission of infection in-utero, and exposure to infectious diseases in the nursery or in the community.
2) The newborn infant may be less capable of responding to infection owing to one or more immunulogic deficiencies.
3) Co-existing diseases of the newborn often complicate the diagnosis and management of neonatal infections for example; acidosis impairs function of polymorph nuclear leuokocytes.
4) Manifestations of infectious diseases in the newborn infant are exremely variable.

5) Transient bacteremia may accompany procedures that truamatize mucosal membranes as endotracheal suctioning, the bacteremia may also occur by direct extension from colonized mucosal surfaces ***(Van den Hoogen et al., 2009).***

6) Distal risk factors for neonatal sepsis include poverty and poor enviromental conditions. Proximate factors include prolonged rupture or membranes,preterm labour,maternal pyrexia, unhygienic intrapartum and postnatal care, low birth weight and pre lactealfeeding of contaminated food and fluids**.**

(Wynn and Wong, 2010)

Mode of infection:

1) **Prenatal infection:** Throughout pregnancy and until the membranes rupture, the fetus is relatively protected from the microbial flora of the mother by the chorioamniotic membranes, the placenta and the antibacterial factors in amniotic fluid, however, there are many ways that infectious agents can reach the fetus to cause infection. Some microbial species cause intrauterine infections that present as congenital infections in the newborn ***(Polin, 2012).***

2) **Natal infection:** The human birth canal is colonized with aerobic and anaerobic organisms. Vaginal delivery inevitably results in contamination and the beginning of colonization of skin and gut of the newborn. The commonest causative

organisms are Group B Streptococci (GBS), gram-negative enteric organism, Staphylococcus aureus and Streptococcus fecalis ***(Stoll et al., 2011).***

3) **Postnatal infection:** It occurs in the delivery room or the newborn nursery via respiratory tract, gastrointestinal tract, umbilical stump, infected circumcision wound. These infections may be transmitted through:

Umbilical or peripheral venous catheters, equipments of resuscitation, inhalation therapy, total parentral nutrition (TPN), or exchange transfusion.

Direct transmission of organisms through the hands of nursery or other adult personnel when hand washing techniques are inadequate ***(Edmond and Zaidi, 2010).***

Classification of neonatal sepsis:

In newborn, neonatal sepsis can be categorized as early or late onset, according to time of onset**.**

Table (3): Classification of Neonatal sepsis:

Points	Early onset sepsis	Late onset sepsis
Incidence	1.5%	25%
Time of presentation	Usually within 12 hr in the first 3-7 d of life	Usually term baby older than 1 wk
Most common pathogen	Group B streptococci Escherichia coli	Coagulase-negative stapylococci
Type of infection	Pnumonia and sepsis (multisystem)	Meningitis with sepsis (focal)
Most acquired from	Mother's birth canal (OB. complications)	Enviromental (rarely OB complication)
Infant gestation	Majority term, but preterm Unusually suscipitable	Majority term
Mortality rate	15-20% or higher with preterm	10-20%
Morbidity	Less long term issues	Late neurodevelpmental sequale

(Stoll, 2008)

1-Early onset sepsis (EONS):

Eighty-five percent of newborns with early-onset infection present within 24 hours, 5% present at 24-48 hours,

and a smaller percentage of patients present within 48-72 hours. Onset is most rapid in premature neonates, The incidence of EONS in term neonates is 1-2/1000 live births with a mortality of 3% ***(Klinger et al., 2009).***

- ***Type of pathogens:***

The microorganisms most commonly associated with early-onset infection include group B Streptococcus (GBS), Escherichia coli, coagulase-negative Staphylococcus, Haemophilus influenzae, and Listeria monocytogenes ***(Klinger et al., 2009).***

- ***Route of infection:***

As shown in fig (1), syndrome is associated with acquisition of microorganisms from the mother. Transplacental infection or an ascending infection from the cervix may be caused by organisms that colonize in the mother's genitourinary tract, with acquisition of the microbe by passage through a colonized birth canal at delivery ***(Anderson, 2012).***

- ***Presentation:***

It has a fulminating course with features of pnumonia and septicaemia predominating ***(Bizzarro et al., 2008).***

Risk factors for early onset neonatal sepsis:

1) Maternal and obstetric risk factors:

a) Prolonged premature rupture of membranes (PROM) for ≥ 18 hours.

b) Chorioamnionitis and maternal fever ≥37.5 C.

c) Maternal colonization with group B streptococci (GBS).

d) Untreated urinary tract infection (UTI**)** due to raising the risk of prematurity and chorioamnionitis.

e) Traumatic or septic delivery after use of obstetric forceps or infection of cephalhaematoma increases the risk of infection in neonates.

f) disturbing the integrity of uterine content:

Amniocentesis, cervical cerclage, and trans-cervical chorionic villus sampling, or percutaneous blood sampling can permit entery of skin or vaginal organisms causing amnionitis and secondry fetal infection.

(Leal et al., 2012)

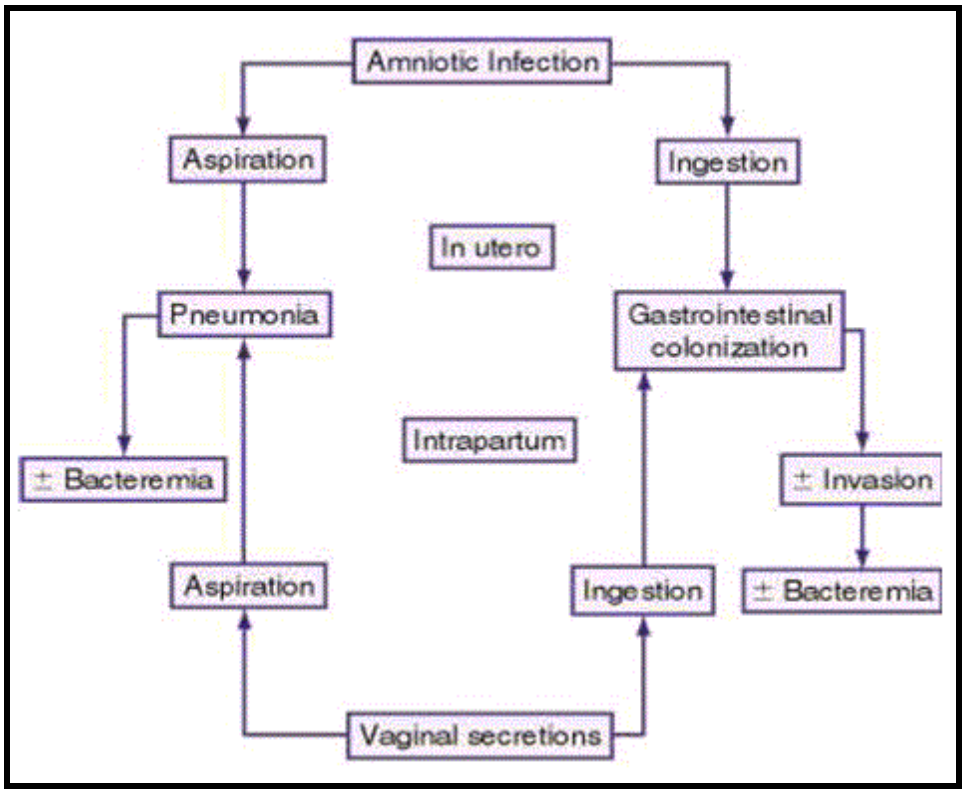

Fig. (1): Pathways of ascending or intrapartum infection ***(Stoll, 2008).***

2) Neonatal risk factors:

a) **Prematurity and low birth weight (LBW):** are the most important neonatal factors predisposing to infection ***(Stoll et al., 2011).***

b) **Sex:** Male neonates have higher incidence of sepsis and meningitis, especially for the gram-negative enteric bacilli than female neonates**.** This suggests the probability of sex linked factor in host susceptibility ***(Leal et al., 2012).***

c) **Race:** Black infants have an increased incidence of GBS disease and late-onset sepsis ***(Anderson-Berry, 2012).***

d) **Apgar score:** A 5 minute score < 7 carries 56 fold risk of sepsis for infants delivered vaginally higher than the infants with higher scores. Apgar score less than 5 at one minute may be due to sepsis, especially with presence of risk factors for infection ***(Shah et al., 2006).***

Table (4): Risk factors with an increased risk of early onset sepsis

1) Low birth weight (<2500 grams) or prematurity.
2) Febrile illness in the mother with evidence of bacterial infection within 2 weeks prior to delivery.
3) Foul smelling and/or meconium stained liquor amnii.
4) Prolonged Rupture of membranes >24 hours.
5) Single unclean or > 3 sterile vaginal examination(s) during labor.
6) Prolonged labor (sum of 1^{st} and 2^{nd} stage of labor > 24 hrs) with instrumentation.
7) Perinatal asphyxia (Apgar score <4 at 1 minute),or difficult resuscitation.

(Jeeva et al., 2008)

Presence of foul smelling liquor or three of the above mentioned risk factors warrant initiation of antibiotic treatment. Infants with two risk factors should be investigated and then treated accordingly ***(Jeeva et al., 2008).***

2- Late-Onset Sepsis (lOS):

Syndrome occurs at 4-90 days of life and is acquired from the care giving environment ***(Anderson, 2012).***

Risk factors of late onset sepsis:

The source of infection is either nosocomial or community acquired an. Risk factors for development of LOS include:

a) **Resuscitation at birth:** particularly if it involves endotracheal intubation, insertion of an umbilical vessel catheter ***(Stoll, 2008).***

b) **Invasive Procedures:** Invasive monitoring of respiratory function, metabolic support as TPN, various drains and shunts for hydrocephalus all increase the risk of sepsis ***(Edmond and Zaidi, 2010).***

c) **Environment:** NICU admission, Increasing survival rates of VLBW infants is prolonging the hospital stay and subsequently exposing infants to late onset infections ***(Malik, 2010).***

d) **Drugs:** Systemic antibiotics potentiate the overgrowth of certain organisms as Staphylococcus epidermidis and also responsible for the emergence of antibiotic-resistant strains ***(Tripathi et al., 2012).***

e) **Administrations of intravenous lipid emulsions:** It decreases the flow rate through IV catheter and potentiates the growth of some microorganisms and Infants with prolonged duration of central catheters and TPN, those with delayed initiation of enteral feeding are all at substantially increased risk of late onset neonatal sepsis ***(Stoll, 2008).***

- **Presentation:**

The clinical manifestations may be acute physiological deterioration or manifestations of a more localized infection in form of pneumonia or meningitis which progress to septicemia ***(Anderson-Berry, 2012)***.

3-Very late-onset sepsis:

Very late-onset sepsis is often caused by Candida species or by commensal organisms such as coagulase-negative staphylococci (CONS) ***(Weisse and Aronoff, 2008)***.

Table (5): Relationship of time of onset of neonatal infection and mode of transmission of infection.

Characteristics	Prenatal	Early onset	Late onset	Late, Late onset
Age at onset	Prior of birth	birth to 7days usually <72hr	7 to 30 days	> 30 days
Maternal/obstetric complication	Common	Common	Uncommon	Varies
Prematurity	Maternal infections, usually primary infection prolonged rupture of membranes	Frequent	Varies	Usual
Organism source	Transplacental or ascending	Maternal genital tract	Maternal genital tract/ environment	Environment/ community
Manifestation	Multi-system	Multi-system	Multi-system or focal	Multi-system or focal
Site	Intra-Uterine	Normal nursery, NICU community	NICU, community	NICU, community

(Stoll et al., 2004)

The commonest pathogens associated with neonatal sepsis:

Bacterial organisms:

a) Gram- positive organisms

1) **GBS**: GBS organism colonizes the maternal gastrointestinal (GI) tract and birth canal. Approximately 25% of women have asymptomatic GBS colonization during pregnancy ***(Anderson, 2012).***
2) **Group A streptoccoci:** The disease caused by this organism varies from a low-grade chronic omphalitis to fulminant disease with severe septicemia and meningitis ***(Edmond and Zaidi, 2010).***
3) **Streptococcus Viridians:** In contrast to neonates with GBS infection, those with Streptococcus Viridans infection present later (mean age 3-5 days). The neonates are less likely to develop leucopenia and respiratory distress ***(Van Den Hoogen et al., 2009).***
4) **Staphylococci, Coagulase negative Staphylococci (CoNS):** The most frequently isolated pathogens in nosocomial and catheter-related bloodstream infections ***(Jeffries et al., 2012).*** Staph aureus is the second most common pathogen causing LOS in NICU infants with VLBW. Methicillin Resistant Staphylococcus Aureus (MRSA) remains a major problem in nosocomial infections.